IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Stefano et al.	**Conf. No.:**	6473
Serial No.:	10/526,091	**Art Unit:**	1655
Filed:	08/15/2005	**Examiner:**	Winston, Randall O.
Title:	NITRIC OXIDE AND ITS BIOMEDICAL SIGNIFICANCE	**Docket No.:**	R1381-200-US (SUNY-0003-US)

DECLARATION UNDER 37 CFR 1.132

I, George B. Stefano, Ph.D., declare the following:

1. I am a co-inventor of the subject matter described and claimed in the above-identified patent application. I am currently employed by the Neuroscience Research Institute, State University of New York/College at Old Westbury, P.O. Box 210, Old Westbury, New York, 11568. A copy of my curriculum vitae is annexed as Exhibit "A".

2. I am fully familiar with the subject patent application and with the final rejection mailed October 6, 2008 and the advisory action mailed February 2, 2009. I understand that the examiner has rejected claims 1-7 and 15-18 under 35 USC 102(e) as allegedly being anticipated by or in the alternative, under 35 USC 103(a) as allegedly being obvious over (PDR for Herbal Medicines, First Edition, *Salix Species*, pages 1111-1112, copyrighted 1998) (referred to herein as "PDR") or (The Healing Herbs, The Ultimate Guide to the Curative Power of Nature's Medicines, *White Willow*, pages 369-371, copyrighted 1991) (referred to herein as "Healing Herbs"). I understand that the basis of the rejection is that the references teach "a pharmaceutical composition which appears

to be the same as that instantly claimed since both the claimed invention and each of the reference compositions comprising a water extract of the bark of the same *Salix alba* species would also inherently contain water soluble components having the claimed molecular weight therein." Office Action 10-02-2008 p.3 I understand that the alternative basis of the rejection is that the invention would have been obvious to a person of ordinary skill in the art "even if the claimed composition is not identical to the referenced composition in regard to some unidentified characteristics, the differences between the that which is disclosed and that is claimed are considered to be so slight that the referenced composition is likely to inherently possess the same characteristics which they have been shown." Id. p.4

3. It is my opinion that the current amendments to claims 1 and 15 reciting, *inter alia*, "wherein said extract contains a first compound with a molecular weight of 263.3 daltons and a second compound with a molecular weight of 356.5 daltons and a third compound with a molecular weight of 337.5 daltons and a fourth compound with a molecular weight of 354.4 daltons" overcome these rejections. The current amendments are supported by the identification of detailed chemical structures of four (4) compounds contained within Healthin II.

4. The determination of chemical structure was accomplished by rigorous comparative analysis of mass spectrometry records obtained from chemical libraries and by our original spectra of Healthin II. We provide detailed reporting of each individual spectral analysis and comparative statistical matches with original spectra obtained from mass spectrometry of Healthin II. The matches are compelling and provide significant support for our contentions that Healthin II contains discrete chemical

compounds that contribute to additive and/or synergistic evoked stimulation of nitric oxide release. The abilities of these combinations of chemical compounds to evoke the therapeutic release of nitric oxide from constitutive positive physiological sources clearly separate their medicinal properties from those that are categorized within the salicin class of compounds.

5. We have found that that Healthin II contains four (4) distinct nitric oxide releasing compounds: 2,3-dihydroxypropyl oleate, bis(m-phenoxyphenyl) ether, 6-acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline, and (+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline.

6. Healthin II represents discrete HPLC peaks that elute at characteristic retention times determined by the concentration of acetonitrile within the HPLC mobile phase. Despite the appearance as single HPLC peaks, Healthin II contains more than one chemical compounds. We know this from the composite MS TOF fragmentation patterns of Healthin II.

7. The mass spectrometry for Healthin II is annexed as Exhibit "B".

8. A description, mass spectrometry and comparative mass spectrometry for 2,3-dihydroxypropyl oleate is annexed as Exhibit "C". 2,3-dihydroxypropyl oleate has a molecular weight of 356.5 daltons.

9. A description, mass spectrometry and comparative mass spectrometry for bis(m-phenoxyphenyl) ether is annexed as Exhibit "D". bis(m-phenoxyphenyl) ether has a molecular weight of 354.4 daltons.

10. A description, mass spectrometry and comparative mass spectrometry for 6-acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline is annexed as Exhibit "E". 6-

acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline has a molecular weight of 263.3 daltons.

11. A description, mass spectrometry and comparative mass spectrometry for (+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline is annexed as Exhibit "F". (+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline has a molecular weight of 337.5 daltons.

12. Data in support of the present application indicates that aqueous extraction procedures utilized in earlier experiments operationally resulted in significant carry over of lipid soluble chemical compounds. This is based on the observed retention of active nitric oxide-releasing components on reverse phase HPLC columns and the ability of a traditional lipid extraction procedure to partition and concentrate these same active compounds. Overall, these results are consistent with the established chemical literature that indicates that nonpolar and lipid compounds are capable of forming mixed micelles within aqueous media. Refer to Exhibit "G" detailing the nitric oxide releasing properties of the claimed pharmaceutical composition.

13. We provide the chemical identities of four (4) nonpolar compounds operationally contained within the HPLC peaks termed Healthin II. The chemical identities of the four (4) compounds were determined by rigorous statistical analysis of composite TOF MS fragmentation spectra of Healthin II in comparison to filed TOF MS fragmentation spectra for each compound. Based on our accumulated chemical validation analyses, the four (4) nonpolar compounds capable of nitric oxide release are novel and clearly distinct from the class of water soluble, hydrophilic, salicin/salicylate compounds previously described by prior art.

I further declare that all statements made herein of my own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issued thereon.

George B. Stefano, Ph.D.

4/8/09
Dated

ATTACHMENT "A"

CURRICULUM VITAE

PART I: **General Information**

DATE PREPARED: Feb 2, 2008

Name: George B. Stefano

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Home Address: 1 Sleepy Lane, Melville, NY 11747

Office Phone: 516-876-2732 **Fax:** (516) 876-2727

E-Mail: gstefano@sunynri.org

Place of Birth: New York City, New York

Education:

1973 Ph.D.	Fordham University
1969 M.S.	Fordham University
1967 B.S.	Wagner College

Academic Appointments:

1999-	Vice Chair, Board of Directors, Research Foundation, State University of New York. Executive Committee of RFSUNY, Finance Committee, Human Resources Committee.
1999-2003	Director, Basic Research, Mind/Body Medical Institute, Boston MA.
1998-2003	Adjunct Professor, Dept. Medicine, Beth Israel Deaconess Medical Center, Harvard Med. School.
1994-	Adjunct Professor, Dept. Marine Sciences, SUNY Stony Brook
1994-	Adjunct Professor, Dept. Biophysics and Physiology, SUNY Stony Brook
1993-1994	Professor (Contracto) Institute of Pathology, Univ. Modena Medical School, Italy
1993-	Adjunct Professor of Surgery, Univ. Medical Center, SUNY Stony Brook.
1989-	**Director, Neuroscience Research Institute, SUNY Old Westbury**
1982-	Distinguished Professor of Biology, SUNY/College at Old Westbury
1979-1982	Associate Professor of Biology, CUNY/Medgar Evers College
1977-1979	Adjunct Associate Professor of Biology, C.W. Post Center, Long Island University
1975-1979	Adjunct Instructor of Medical Physiology-Pharmacology, Montefiore Hospital and Medical Center
1972-1979	Assistant Professor of Biology, CUNY/New York Technical College
1971-1972	Instructor of Anatomy and Physiology, Histology, CUNY/Queensborough Community College

1971-1972	Adjunct Instructor of Anatomy and Physiology, Pace College
1969-1970	Instructor of Anatomy and Physiology, Histology, CUNY/Bronx Community College

Other Professional Positions and Major Appointments:

2006-	Professor, Pain Center, Sino-Japanese Friendship Hospital, Beijing, PR China
2006-	Professor, Peking University, PR China
2006-	Chief Consultant for Technologies, PR China
2003-	Acting Vice President for Research, SUNY Farmingdale
2002-	Board Member, Broad Hollow Bioscience Park, Inc.
1998-	Research Associate, Invertebrate Neuroimmune Laboratory, UPRESA CNRS, University of Sciences & Technology of Lille, France
1995-1998	Director, Cardiac Research Program, Cardiovascular Research Center, SUNY Medical Center at Stony Brook
1994-1996	Research Associate, Div. Psychiatry, Brigham and Women's Hosp., Harvard Medical School
1979-1982	Research Coordinator, Department Anesthesiology, St. Joseph's Hospital
1978-1979	Biochemical Project Director, Malignant Hyperthermia Center, Montefiore Hospital and Medical Center
1977-1981	Research Consultant, Department of Pharmacology, University of West Virginia School of Medicine.
1977-1981	Research Associate, Department of Natural Sciences, CUNY/Medgar Evers College
1976	Invited Researcher, Biology Research Institute, Tihany, Hungary.
1975-1979	Research Consultant, Department of Neurology, Albert Einstein College of Medicine
1973-1980	Research Associate, Department of Biological Sciences, Fordham University.

Major Administrative Responsibilities:

2002-	SUNY-wide Patent Committee member.
2000- 2003	Board of Trustees, Wagner College
1999-	Vice Chair, Board of Directors, Research Foundation of the State University of New York
1994	Acting Vice Pres. for Academic Affairs at SUNY Old Westbury
1989-	**Director, Old Westbury Neuroscience Research Institute**
1988-	Director, Multidisciplinary Center for the Study of Aging
1985-1988	Assistant Vice President for Research, SUNY/College at Old Westbury
1982-1986	Chair, Biological Sciences Dept, SUNY/College at Old Westbury

Major Committee Assignments:

State University of New York/College at Old Westbury and related academic institutes:

2007	Chair, Committee on Research for the RF of SUNY

1995-2003	Chair, Radiation Safety Committee
1994	Chair, Vice President for Academic Affairs Selection Committee
1990	Drug Abuse Committee
1990	College Budget Committee
1990	Chair, Internal Grant Review Comm.
1988-1990	Scientific Conduct Committee
1985-1988	Co-Chair, Science Building Committee
1985-1987	Computer Policy Committee
1984-1987	Science Space Allocation Committee
1984-1985	Long-Range Institutional Planning Committee
1983-1988	College-wide Reappointment, Promotion and Tenure Committee
1983-1986	Conveners Committee
1983-1985	President's Advisory Committee
1983-1985	Chairman, Institutional Grant Committee
1983	Judicial Review Committee

National and Regional:

1999	President, Advances in Neuroimmunology Meeting, Shanghai, China
1999	Co-organizer, Neuroimmune Congress, Shanghai, China
1997	Organizer/Chairman, NIMH-COR Colloquium
1997	Co-organizer, Neuroimmune School, Univ. Lille/SUNY-Old Westbury
1997	Coordinator, Neuroimmune Congress, Beijing Medical University, China
1996	Coordinator, Neuroimmune Summer School, Rimini, Italy
1996	Co-chair, Psychoneuroimmune Consortium: Opiate Immunoregulatory Processes, SUNY-Old Westbury & Div. Psychiatry, Brigham and Women's Hosp.
1995	Organizer, Neuroimmune delegation by invitation of the People's Republic of China to visit various medical universities in China
1994-1996	Co-Director, Psychoneuroimmune Consortium, Div. Psychiatry, Brigham and Women's Hosp. Harvard Medical School
1994	Organizer, Cardiopulmonary Bypass and Neuroimmune Implications Symposium
1992	Organizing Committee, Stress Workshop, Modena, Italy
1992	Chair, Neuroimmune Neuropeptide Receptor Section of Satellite Symposium on Neuroimmune Interactions and their Regulation, Budapest, Hungary
1991	Organizer, Neurochemistry Workshop with NIDA and industry (BAS, American Innovision, Inc., Morrell Inst. Co.)
1991	Executive President, International Association of Immuno-Neurobiologists, France
1990-1991	Secretary/Chair, National Conference Subcommittee, National Science Literacy Conference of Dr. Louis Sullivan, PHS
1990	Headed major session of Comparative Neuroimmunology-Neuroimmunomodulation Congress, Florence, Italy
1990	Co-organizer, Comparative and Developmental Neuroimmunology Workshop, Modena, Italy

1989	Co-organizer, Neuropeptide/Neuropharmacology Meeting, West Germany
1987-1992	President, ADAMHA-MARC Program Directors Association
1987	Presenter, 2nd Neuroscience World Congress, Budapest, Hungary
1987	Organizing Committee, Invertebrate Neurobiology Symposium: Neurotransmitters/Modulators and Receptors, Tihany, Hungary
1987	Executive Committee, NIH-MBRS Centennial
1987	Consultant, NIMH/NIDA Committee to enhance neuroscience training and programs productivity
1986-1990	Organizer, ADAMHA-MARC Washington Conference
1984	Organizer for SUNY/Old Westbury, Comparative Opioid Neuropeptide Meeting
1983	Invited Consultant, Drug Abuse-New York City, Councilman J. O'Donnovan
1980	International Organization Committee, Satellite Symposia: "Neurotransmitters in Invertebrates; Chairman of Peptidergic-Neurobiology Session, Vezyprem, Hungary
1980	Chair and presenter, Scientific Session at International Physiology Congress Meeting, Budapest, Hungary
1978-1984	Director of East Coast Neuroscience Foundation, Inc; Chairman, Neuropharmacology Division

Current Grant Review Committees

National Institute of Mental Health
National Science Foundation
National Institute on Drug Abuse
National Heart, Lung and Blood Institute

Current Journal Review Committees

Science
Nature
Brain Research
Journal of Neuroimmunology
Journal of Immunology
Life Sciences
Cellular and Molecular Neurobiology
Molecular Brain Research
Endocrinology
Neuroendocrinology
Neuroscience Letters
Cell and Tissue Research
FEBS Letters
Journal of Biological Chemistry
Neurochemistry
Journal of Neurochemistry

Professional Societies:

President of the Morphine Research Society 2005-.
New York Academy of Science
American Association for the Advancement of Science
International Society for Invertebrate Neurobiology (Seat on Executive Council)
International Society of Neuroimmunology
Society for Neuroscience
Gerontology Society of America
Member of the Council on Undergraduate Research

Editorial Boards:

2002-	Deputy Editor, Neuroendocrinology Letters
2002-2003	Co-Editor in Chief, Placebo
2001-	International Journal of Molecular Medicine
2001-	Editor in Chief -Medical Science Monitor
2000-2001	Editor, Animal Biology
1999-2000	Progress in NeuroEndocrinImmunology
1999-	Editor, Modern Aspects of Immunobiology, IA-Verlag
1999-	Advisory Board and Editor for North America, Acta Pharmacologica Sinica
1998-1999	Associate Editor, Journal of Neuroimmunology
1990-1996	Co-Editor & Founder, Advances in Neuroimmunology, Pergamon Press
1987-1992	Editor, STIMULUS, ADAMHA-MARC newsletter
1979-	Editorial Board & Founder, Cellular and Molecular Neurobiology, Plenum Press
1978-1984	East Coast Neuroscience Foundation, Inc. Bulletin Division

Awards and Honors:

2006	Excellence in Education, Old Westbury Alumni Association
2004	First Patent Award, Research Foundation of SUNY
2003	Award for Excellence in the Pursuit of Knowledge, Research Foundation of SUNY
2000	International Educators Award, Long Island International Business Forum
1994	Rod Spence Research Award
1991	CASE Professorship of the Year Award for New York State
1989	Distinguished Teaching Professor Status, State University of New York
1988	Honorary membership, Hungarian Academy of Science, Physiology Society and Samuel Racs Medallion
1983	Alumni Achievement Award, Wagner College
1967-1969	Graduate Assistantship, Department of Biology, Fordham University
1965-1969	Scholar Incentive Award, NYS Department of Education

PART II: Research and Teaching

A. Narrative report:

Dr. George Stefano, a Distinguished Teaching Professor, serves as the Director of the Neuroscience Research Institute at the State University of New York (SUNY) College at Old Westbury. This is one of many four-year Liberal Arts Colleges within the SUNY system, and the only one with a specific minority mission: to foster science education and research career options for these students. Dr. Stefano serves as the Director of Basic Research for the Mind/Body Medical Institute of the Beth Israel Deaconess Medical Center in Boston. Dr. Stefano is also the Vice Chair of the Board of Directors of the Research Foundation of SUNY. Four of his minority students have honored with the Chancellor's Award for Academic Excellence and 15% of his publications are co-authored by his students.

Dr. Stefano has published over 300 papers in peer reviewed journals, i.e., Science. He has edited four books and over 50 chapters for various texts. He has four patents. Since 1978, his research is funded by the National Institute of Mental Health, National Institute on Drug Abuse, National Institutes of Health, Fogarty International Center, National Science Foundation, Center for Disease Control and Prevention, and various other private foundations. Dr. Stefano has serves as the Editor and/or Associate Editor of various scientific journals, i.e., Modern Aspects of Immunobiology. He has also organized over eight National and International Conferences and was recently elected president of the International Morphine Research Society in Italy.

His discoveries include, and are not limited to, the following: 1) novel opiate receptors coupled to nitric oxide release in human tissues; 2) estrogen cell surface receptors coupled to nitric oxide release in human tissues; 3) morphine is an endogenous signal molecule found in human tissues; 4) mollusks have similar opiate processes, thus it has been conserved during evolution; 5) cannabinoid coupled nitric oxide receptors found in human and invertebrate tissues; 6) endogenous morphine is made by human and animal parasites to escape host immunosurveillance.

The implication of his patents and discoveries demonstrate that morphine is made in animal tissues and it serves as a signal molecule to down regulate tissues that have been hyper-excited. This is supported by his discovery of a novel μ3 opiate receptor that specifically uses morphine as its activator. Thus, immune, vascular, and neural hyper-excitation can be brought under control by using this naturally occurring signal molecule. Supporting this hypothesis are the findings from Dr. Stefano that animal parasites, including human parasitic worms, make morphine presumably to down regulate the host immune response allowing the parasite to proliferate in its animal host. The importance of this morphine system has been enhanced by the discovery of this molecule and its corresponding receptor in animals that evolved 500 million years before man.

Recently, Dr. Stefano has extended this line of study to include estrogen signaling, which also results in nitric oxide release. Furthermore, he has demonstrated that this signaling occurs via cell surface receptors, not through a DNA based process, as most investigators believed. With this in mind, Dr. Stefano's career is founded on great creativity coupled to perseverance, all in the face of conventional wisdom.

B. Funding Information:

(Funding from individuals and organizations of less than $25,000 are not included)

2000-2003	CDC Mechanisms and Therapeutic Effects of the Relaxation Response	Co-PI
1999-2002	NIMH/MRISP Neurobiology of Morphine	PI
1998-2001	NIMH High School Honors Research Program.	Prog Dir
1992-1996	NSF Teacher-Science Training Award	Co-PI
1991-2001	NIMH/COR Opioid Mechanisms in Neuroimmunology.	Prog Dir
1990-1993	NIDA/ADAMHA Opioid Autoimmunoregulatory Mechanisms	Prog Dir
1990	SUNY Scientific Equipment Grant	PI
1988-1991	NSF International Opioid Neurobiology	Prog Dir
1987-1991	NIH Grant 08180 Effect of Physical Stress on the Opioid-Dopaminergic Interaction in Invertebrates	PI
1987	RF of SUNY Scientific Equipment Grant	Co-PI
1987	NIH Scientific Equipment Grant	PI
1986-1991	NIMH/ADAMHA-MARC Undergraduate Honors Research Training Grant	Prog Dir
1985-1989	NYS Dept. of Ed. Title III Computer Development Grant.	Co-Assoc Prog Dir
1984	NIH Scientific Equipment Funding	PI
1983-1986	NIMH/ADAMHA-MARC Undergraduate Training - Narcotic Mechanisms	Prog Dir
1983-1986	NIH/MBRS Dopamine-Opioid Interaction	PI
1979-1983	NIMH/MBS Grant RR08171 Opioid Peptide Metabolism	PI

Corporate Partnerships (National Faculty Training Workshops for NIDA):

2000	Nikon Inc., Image Analytics, Morrell Inst. Company Opiate Vscular Neuroimmunology (Chicago, IL)
1999	Nikon Inc., Image Analytics, Morrell Inst. Company Opiate–AIDS Interaction (Melville, NY)
1998	Nikon Inc., Image Analytics, Morrell Inst. Company Cannabinoids and Opiate Vascular Neuroimmunology (Chicago, IL)
1994-1997	Nikon Inc., Image Analytics, Morrell Inst. Company Endogenous Morphine / Image Analysis Workshop (Melville, NY)

1993	Nikon Inc., Image Analytics, Morrell Inst. Company Morphine in Neuroimmunology / Image Analysis Workshop (Melville, NY)
1993	KNOGO Corporation The Effects of Electromagnetic Radiation on Immunocytes
1992	American Innovision AIDS: Neuroimmunology / Image Analysis Workshop (San Diego, CA)
1991	BAS Instruments, Morrell Inst. Company Neurochemistry Workshop.(Cherry Hill, NJ)

C. Report of Current Research Activities

2002-2007	NIMH/MRISP Endogenous Morphine	PI
2002-2006	Lifewaves Inc. Cyclic Activation/Relaxation Exercise	Sub-Proj Co-PI
2002-2006	Cell Dynamics Inc. Solubilzation and Isolation of Plant Extracts	Co-PI
1994-2008	NIDA/MIDARP Opiate Neuroimmune Mechanisms	PI
1993-2009	NIH/Fogarty Minority International Research Training Program	Prog Co-Dir

Patents

Mu3 Opiate Receptor	09/530,880
Mu3 Expression on Human White Blood Cells	US09/05452
Parasite Infections	60/369,641
Placebo Effect & Relaxation Response	US02/00941

D. Report of Teaching (Summary)

1. Local Contributions, SUNY College at Old Westbury

Dr. Stefano's primary responsibilities at the State University of New York, Old Westbury, are directed toward instruction and research. However, believing that research involves teaching, he has been able to combine the two objectives into one activity. In this regard, he has instructed undergraduates in the following courses: a) Cell Biology; b) Histology; c) Biology of Aging; and d) Cellular and Molecular Neurobiology. In these courses, over the past 20 years, the laboratory exercises have consisted of real research questions that have enabled his students to pursue these questions as a research topic as well. Indeed, at least 20% of his publications include the names of these students as coauthors. Furthermore, many of these students were minorities traditionally under-represented in the sciences. To further their career research/biomedical goals they were also part of various grants Dr. Stefano has directed to support minority participation in research. In the last four years, four of his students have been honored with the Chancellor's Award for Academic Excellence, a SUNY-wide competition. In addition to these activities, he has taught neuroimmunology to medical students at the University

of Modena. Based, in part, on this high level of instruction, Dr. Stefano has been awarded the highest academic rank at SUNY, namely, Distinguished Teaching Professor.

2. Regional, National, and International Contributions and Invited Presentations

2001	Plenary Speaker Immune Congress, Modena, Italy
2000	Lecture, Opiate Neurovascular Regulation CUNY Queens College
2000	Lecture, Opiate Immunomodulation SUNY Upstate
1999	Lecture, Peripheral Immunovascular Regulation Mind-Body Medical Institute, Harvard Medical School
1998	Invited Speaker, Drugs of Abuse, Immunomodulation and AIDS Chaired Session of Molecular Mechanisms of Immunomodulation Member of Panel, What are the effects of illicit drugs on the immune system as judged by animal models?
1998	Lecture, Opioid Peptide Immunomodulation CUNY Queens College
1998	Lecture, Opiate Immunomodulation Univ. TX, Med. Branch, Galveston
1997	Invited Professor for lecture series University of Sciences & Technology of Lille, France
1996	Lecture, Opiate coupling to Nitric Oxide Release CUNY Queens College
1996	Lecture Series, Cardiothoracic SUNY Stony Brook Univ. Med. Ctr
1995	Plenary Speaker, Neurosecretion Congress, Kiel, Germany
1995	Invited Lead Speaker, Neuroimmune Delegation Beijing Medical Univ.; Peking Union Medical College; West China Med. School; Jinan University and Shanghai Research Institute
1995	Speaker, Neurobiology Meeting, Tihany, Hungary
1995	Speaker, Comparative Immunology Meeting, Breckenridge
1994	Invited Lecturer, Novel Opiate and Opioid Receptors on Human Immunocytes International Neuroimmune Symposium on Infectious Diseases, Rio de Janeiro, Brazil
1993	Lecture, Morphine: A New Class of Signal Molecules Div. Psychiatry, Brigham and Women's Hosp., Harvard Med. School
1993	Lecture, Endogenous Morphine Dept. Psychiatry, Univ. TX, Med. Branch, Galveston
1991	Lecture, Opioid Neuroimmune Mechanisms Institute Pasteur
1991	Lecture, Computer Assisted Microscopy: Neuroimmunology Univ. Texas. Med. Branch at Galveston.
1990	Lecture, Opioid-Neuroimmune Dept. Psychiatry, Univ. TX, Galveston

1990	Lecture, Opioid Neuroimmune Mechanisms Institute Pasteur
1990	Invited Plenary Lecturer, Neuroimmunology European Comparative Endocrinology Society, Belgium
1986	Lecture, Serotonin Fordham University
1985	Invited Major Speaker, Biology of Aging, Neurotransmitters Gordon Research Conference
1983	Invited presenter, Opioid Binding Report Comparative Endocrinology Society Meeting, Sheffield, England
1981	Invited presenter, at: Satellite Symposia-Comparative Neuropharmacology; International Pharmacology Congress, Japan; International Narcotic Research Club, Kyoto, Japan
1980	Invited presenter, Neurobiology of Invertebrates Satellite Symposia-Mechanisms of Integration, Tihany, Hungary

PART III: Bibliography

A. Books, Texts

1. Stefano GB. Comparative Opioid and Related Neuropeptide Mechanisms. Boca Raton, FL: CRC Press, 1986.

2. Stefano GB. Neurobiology of *Mytilus edulis*. Manchester: University of Manchester Press, 1990.

3. Stefano GB, Florey E. Comparative Aspects of Neuropeptide Function. Manchester: University of Manchester Press, 1991.

4. Makman MH, Stefano GB. Neuroregulatory Mechanisms in Aging. Oxford, England: Pergamon Press, 1993.

5. Scharrer B, Smith EM, Stefano GB. Neuropeptides in Neuroimmunology. Heidelberg, Germany: Springer, 1994.

6. Stefano GB. Biomedical Significance of Nitric Oxide. Warsaw, Poland: Medical Science International, 2003.

7. Stefano GB, Bernstein S, Minsun K. Musical Healing. Warsaw, Poland: Medical Science International, 2003.

8. Stefano GB, Benson H, Fricchione GL, Esch T. The Stress Response: Always good and when it is bad. Medical Science International: New York. 2005.

B. Education Articles

1. Stefano GB, Leung MK. An undergraduate minority research training program. J. Coll. Science Teaching. 15: 544-546. 1986.

2. Stefano GB, Pryor SC. An easily accessible alternate animal for studying living cells: Image analysis for undergraduate and high school research. J. Coll. Science Teaching. 1994.

3. Stefano GB, Pryor SC. Image analysis for undergraduate research. Council on Undergraduate Research Quarterly. 1996.

C. Chapters in Research Texts

1. Rozsa KS, Hiripi L, Stefano GB. Pharmacological and biochemical properties of opiate receptors in molluscs. In: Wollemann M, editor. Symposium on biogenic amines and peptide receptors. Hungarian Press, 1979.

2. Rozsa KS, Hiripi L, Stefano GB. Pharmacological and biochemical properties of opiate receptors in the brain of molluscs. In: Vizi ES, Wollemann M, editors. Aminergic and peptidergic receptors. London: Pergamon Press, 1979: 115-131.

3. Stefano GB, Hiripi L, Rozsa KS, Salanki J. Behavioral effects of morphine on the land snail *Helix pomatia*: Demonstration of tolerance. In: Salanki J, editor. Neurobiology of Invertebrates. New York: Pergamon Press, 1980: 285-295.

4. Stefano GB, Kream RM, Zukin RS, Catapane EJ. Seasonal variation of stereospecific enkephalin binding and dopamine responsiveness in *Mytilus edulis* pedal ganglia. In: Rozsa KS, editor. Neurotransmitters in Invertebrates. London: Pergamon Press, 1980: 453-459.

5. Stefano GB. Opiates and neuroactive pentapeptides: Binding characteristics and interactions with dopamine stimulated adenylate cyclase in the pedal ganglia of *Mytilus edulis*. In: Rozsa KS, editor. Neurotransmitters in invertebrates. London: Pergamon Press, 1980: 423-453.

6. Stefano GB, Kream RM. The calcium-dependent neuronal release of dopamine and its antagonism by lithium: Effects of lithium on opiate agonist and antagonist binding in the marine mollusc *Mytilus edulis*. In: Emrich HM, Aldenhoff JB, Lux HD, editors. Basic mechanisms in the action of lithium. Excerpta Medica Press, 1982: 64-71.

7. Stefano GB, Zukin RS, Kream RM. Tentative identification of high affinity opioid binding sites in the pedal ganglia of the marine mussel *Mytilus edulis*. In: Takagi H, Simon EJ, editors. Advances in endogenous and exogenous opioids. New York: Elsevier Science, 1982: 48-50.

8. Kream RM, Leung MK, Stefano GB. Is there authentic substance p in invertebrates? In: Stefano GB, editor. Comparative opioid and related neuropeptide mechanisms. Boca Raton: CRC Press,Inc., 1984: 65-72.

9. Makman MH, Stefano GB. Marine mussels and cephalopods as models for study of neuronal aging. In: Mitchell DH, Johnson TE, editors. Invertebrate models in aging research. Boca Raton,Florida: CRC Press,Inc., 1984: 165-190.

10. Colon-Urban R, Stefano GB. Behavioral effects of morphine on several species of bryozoans. In: Nielson C, Larwood GP, editors. Bryozoa:Ordovician to recent. Denmark: Olsen and Olsen, 1985: 67-71.

11. Hiripi L, Salanki J, Stefano GB, Assanah P. Heavy metal pollution influences serotonin level and dopamine- stimulated adenylate cyclase activity in the CNS of molluscs. In: Salanki J, editor. Symposia Biologica Hungarica. Budapest: Acad.Hungaria Press, 1985: 401-412.

12. Bianchi CP, Wang Z. Morphine enhancement of the cholinergic response of anterior byssus retractor muscle of *Mytilus edulis*. In: Stefano GB, editor. Handbook of opioid and related neuropeptide mechanisms. Boca Raton: CRC Press, 1986: 59-64.

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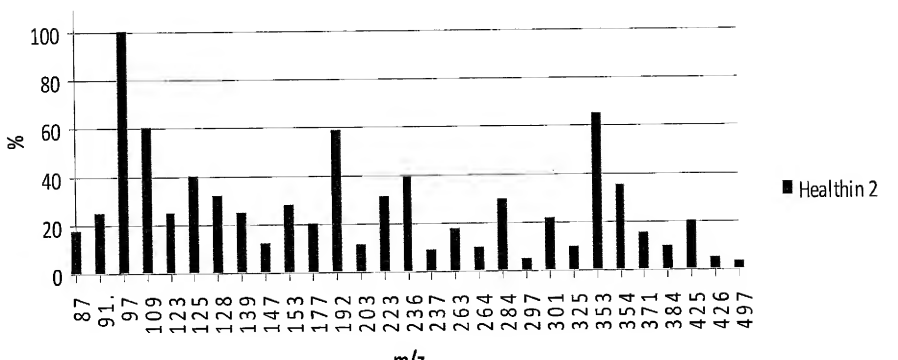
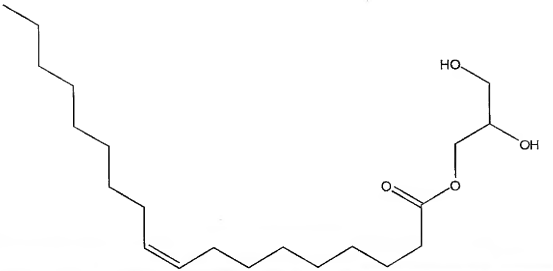
ATTACHMENT "B"

Healthin 2
Mass Spectrometry



ATTACHMENT "C"

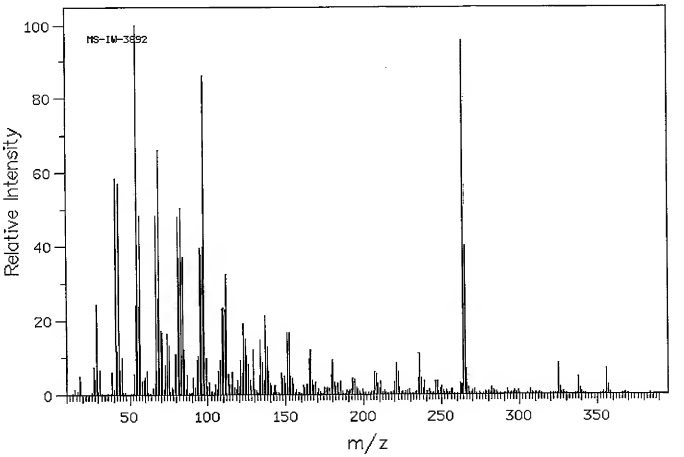
2,3-dihydroxypropyl oleate



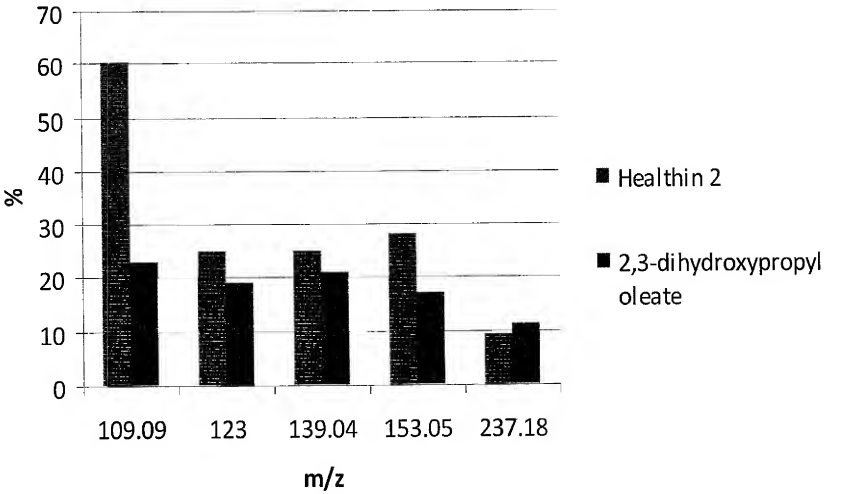
Compound Name:	Molecular Weight:	356.5
	Molecular Formula:	$C_{21}H_{40}O_4$

2,3-dihydroxypropyl oleate
2,3-dihydroxypropyl cis-9-octadecenoate
alpha-monoolein
monoolein
glycerol 1-monooleate

2,3-dihydroxypropyl oleate
Mass Spectrometry

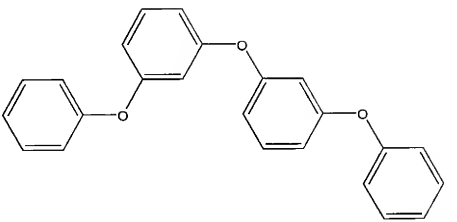


Comparative Mass Spectrometry Analysis



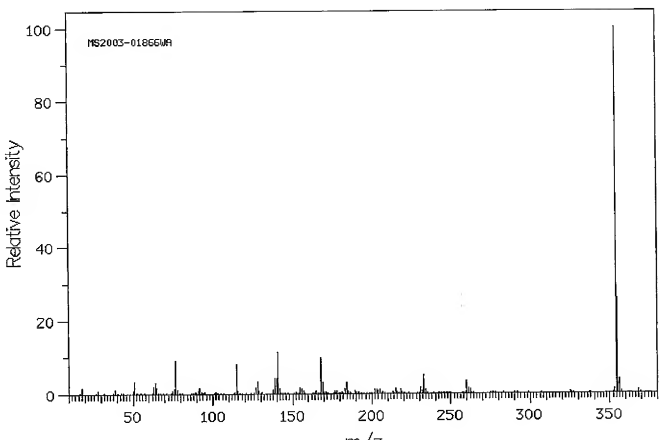
ATTACHMENT "D"

Bis(m-phenoxyphenyl) ether

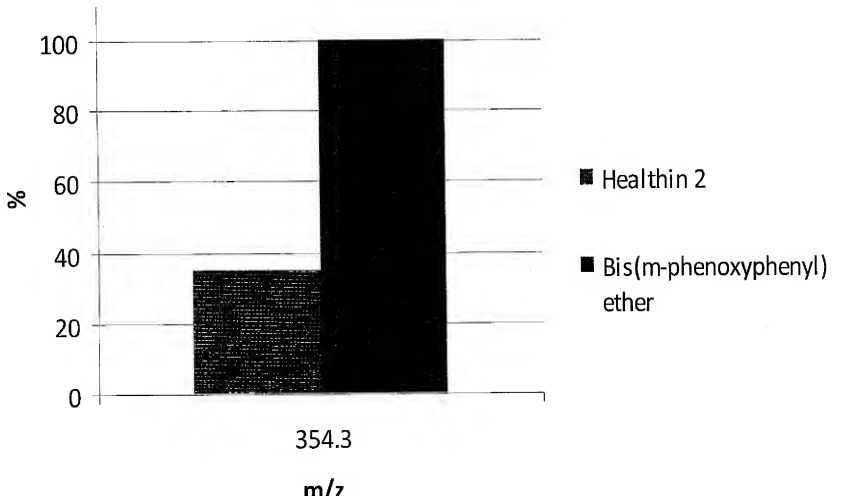


Compound Name:	Molecular Weight:	354.4
	Molecular Formula:	$C_{24}H_{18}O_3$
Bis(m-phenoxyphenyl) ether		

Bis(m-phenoxyphenyl) ether
Mass Spectrometry

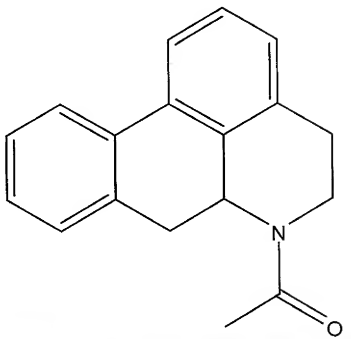


Comparative Mass Spectrometry Analysis



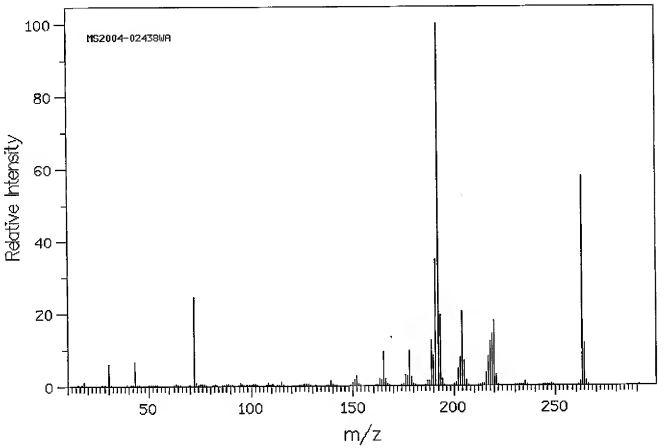
ATTACHMENT "E"

6-acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline

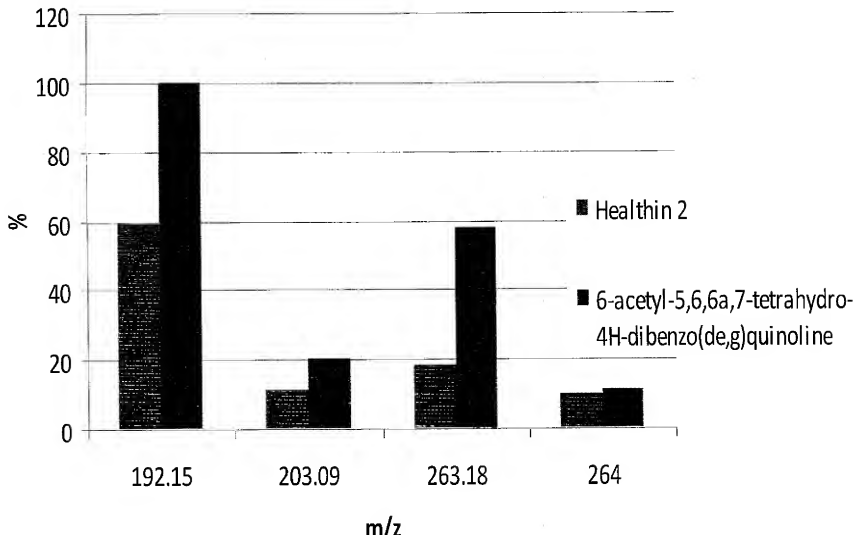


Compound Name:	Molecular Weight:	263.3
	Molecular Formula:	$C_{18}H_{17}NO$
6-acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline		

6-acetyl-5,6,6a,7-tetrahydro-4H-dibenzo(de,g)quinoline
Mass Spectrometry

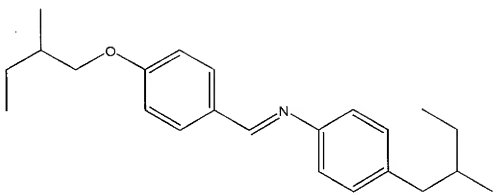


Comparative Mass Spectrometry Analysis



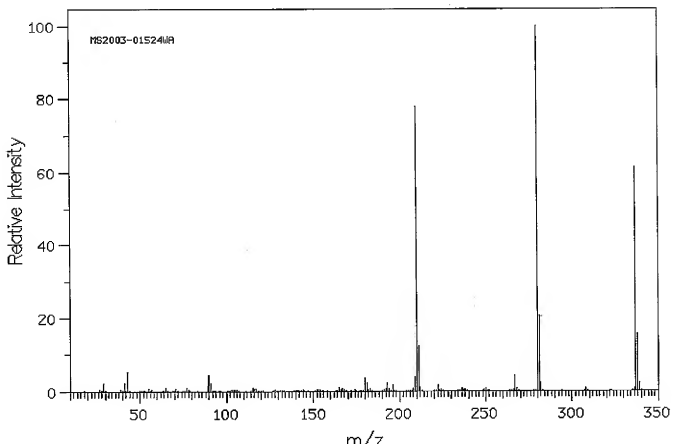
ATTACHMENT "F"

(+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline

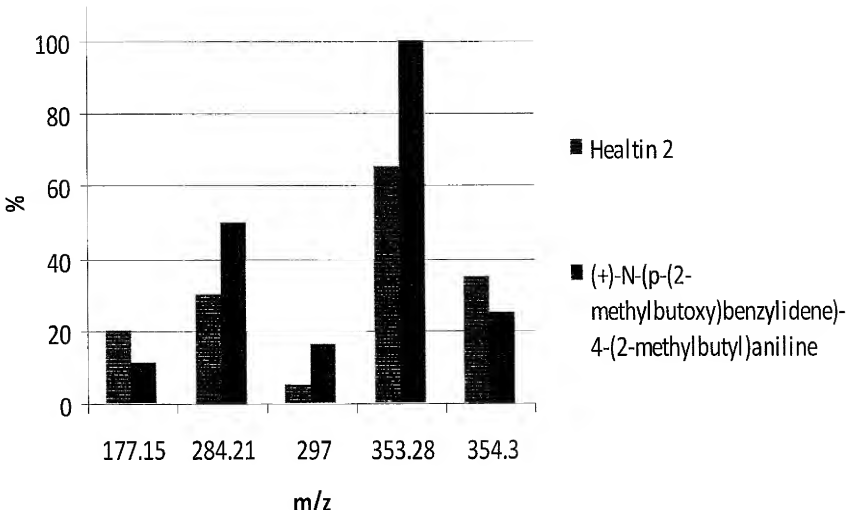


Compound Name:	Molecular Weight:	337.5
	Molecular Formula:	$C_{23}H_{31}NO$
(+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline		

(+)-N-(p-(2-methylbutoxy)benzylidene)-4-(2-methylbutyl)aniline
Mass Spectrometry



Comparative Mass Spectrometry Analysis



ATTACHMENT "G"

Nitric Oxide Releasing Properties of an Organic Extract of White Willow (Salix Alba) Bark

Background and Significance:

Traditional aqueous extractions of white willow bark have yielded herbal medicinal preparations with significant anti-pyretic, anti-inflammatory, and analgesic properties. The medicinal/therapeutic properties of white willow bark extracts have been attributed to water soluble molecules classified as non-steroidal anti-inflammatory drugs (NSAIDs). Prominent white willow bark NSAIDs include salicin [2-(Hydroxymethyl)phenyl β-D-glucopyranoside] and salicylic acid [2-hydroxybenzoic acid]. Historically, the prototype NSAID aspirin [acetylsalicylic acid; 2-acetyloxybenzoic acid] was synthesized via chemical acetylation of salicylic acid obtained from willow bark.

We have recently described novel chemical components of white willow bark extracts with marked therapeutic potential. Specific HPLC fractions of white willow bark extracts have been demonstrated to evoke release of the therapeutically beneficial free radical gas nitric oxide (NO) from ex vivo tissue preparations. Importantly, the temporal profile of NO release indicates selective stimulation of constitutive NO Synthase (cNOS), the NOS isozyme responsible for normal health-related vascular and organ function. Finally, QTOF mass spectroscopic analysis of active NO-releasing HPLC fractions indicate a lack of chemical identity with previously characterized salicin and salicylate analogs found in white willow bark. These data strongly support the existence of a novel class of non-salicin/salicylate therapeutic chemicals in white willow bark that displays an independent mode of action from that established for the pharmaceutical class of salicin/salicylate NSAID agents.

To provide additional confirmatory biochemical evidence that white willow bark contains novel class of non-salicin/salicylate anti-inflammatory compounds, we employed a traditional lipid extraction to selectively eliminate water soluble salicin/salicylate-related chemical compounds. Additionally, parallel water extractions were performed according to specifications listed in two prior art documents. Aliquots from lipid and water extracted white willow bark were tested for biological activity via evoked release of NO from nervous tissue.

White Willow Bark Extraction of Lipid Soluble Compounds:

White willow bark was extracted according to a standard lipid purification protocol. A 10% extraction preparation employed 2g of pulverized white willow bark incubated in 20 ml of organic solvent consisting of chloroform/2-propanol (ratio of 9:1) for 8 hrs at 4o. Supernatant fractions were collected by centrifugation and vacuum dried utilizing a Centri-Vap apparatus. Dried extraction residues were resuspended by sonication in cold PBS (phosphate

buffered saline, pH 7.4) and clarified by centrifugation. Aliquots of clarified white willow bark lipid extracts were tested for their ability to release NO from ex vivo tissue preparations (below).

White Willow Bark Water Extraction:

To demonstrate that NO releasing constituents of white willow bark are exclusively associated with lipid soluble fractions, a traditional water extraction was performed. Two water extraction procedures were employed according to established prior art: 1) a 10% extraction of 2g of pulverized white willow bark incubated in 20 ml dH2O for 8 hrs at room temperature, ref a. below; 2) a 10% extraction of 2g of pulverized white willow bark incubated in 20 ml of boiling dH2O followed by natural cooling at room temperature, ref b. below. Extractions were clarified by centrifugation and supernatants were reserved and freeze dried. Dried samples were reconstituted in PBS and aliquots were tested for their ability to release NO from ex vivo tissue preparations (below).

Real-time Nitric Oxide Release Assay:

Nitric oxide releasing activities of aliquots of clarified white willow bark lipid extracts were determined using a standardized ex vivo invertebrate neural tissue preparation in use in the laboratory for over ten years. For each independent analysis, 10 *Mytilus edulis* pedal ganglia (1-1.2 mg, wet weight/ganglia) were dissected on ice and placed in a 1.7-ml low-binding, pre-siliconized, microcentrifuge tube containing 1 ml of PBS. Nitric oxide release was directly measured using a NO-specific amperometric probe (30 µm, 0.5 mm, World Precision Instruments, Sarasota, FL). The amperometric probe was allowed to equilibrate for 10 minutes in the incubation medium (tissue-free) before being transferred to the tube containing the tissue, and allowed to equilibrate for another 5 minutes. A micromanipulator (World Precision Instruments, Sarasota, Fl), which is attached to the stage of an inverted microscope (Nikon Diaphot, Melville, NY), was used to position the amperometric probe 15 µm above the tissue. NO released from each nervous tissue preparation was quantified using an Apollo 4000 Free Radical Analyzer with an NO-selective amperometric nanoprobe and proprietary software. A linear standard function was constructed from the measured amperiometric responses provided by predetermined concentrations of the NO donor S-nitroso-N-acetyl-DL-penicillamine (SNAP) in the presence of 0.1M CuCl2.

Results:

Aliquots of a reconstituted white willow lipid extract evoked the release of NO from pooled *Mytilus edulis* pedal ganglia in a concentration dependent manner. Typically, a 20ul aliquot equivalent to 2 mg of extracted white willow bark engendered release of NO into the tissue bath at a peak concentration of 10nM equivalent to1nM/ganglia (Figure 1, upper solid trace). In marked contrast to the lipid extraction protocol, a 20ul aliquots equivalent to 2 mg of both cold and

boiling water extracted white willow bark were observed to be without effect on evoked release of NO from pooled ganglia (lower broken traces).

Figure 2 depicts a dose response relationship of lipid extracted white willow bark to evoked release of NO from pooled M. edulis pedal ganglia. 10, 20, and 30ul aliquots equivalent to 1, 2, and 3 mg equivalents of lipid extracted white willow bark engendered release of NO into the tissue bath at a peak concentrations of 4,10, and 12 nM, respectively. Similar results were observed for 3 independent experiments utilizing pooled pedal ganglia.

Aliquots of both cold and boiling water extracted white willow bark equivalent to 1, 2, 5, and 10mg of white willow bark (replicated 3 times) were observed to be without effect on evoked release of NO from pooled ganglia and produced similar time dependent negative responses as depicted in Figure 1(lower broken traces). Finally, control experiments demonstrated that equivalent aliquots of lipid extractable white willow bark added to PBS alone in the absence of pedal ganglia did not produce amperometric responses indicative of non-specific activation of the measurement electrode (not shown).

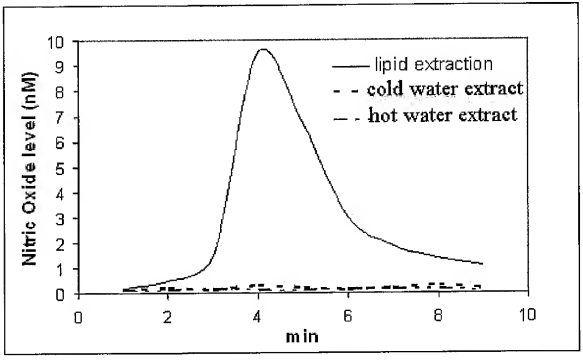


Figure1. Real-time evoked release of NO from pooled M. edulis pedal ganglia by a white willow bark lipid extract in comparison to cold and boiling water white willow bark water extracts. A 20ul aliquot equivalent to 2 mg of lipid extracted white willow bark engendered release of NO into the tissue bath at a peak

concentration of approximately10nM equivalent to1nM/ganglia (upper continuous trace). In marked contrast to the lipid extraction protocol, 20ul aliquots equivalent to 2 mg of cold and boiling water extracted white willow bark were observed to be without effect on evoked release of NO from pooled ganglia (lower broken traces).

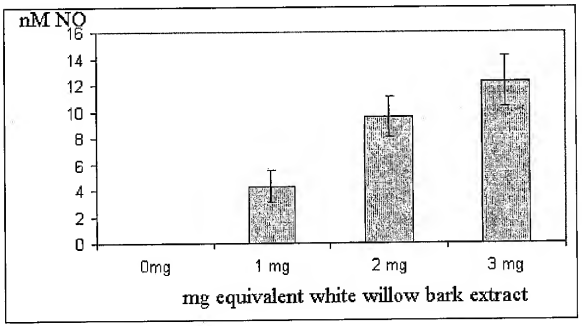


Figure 2. Dose Response relationship of extracted white willow bark to evoked release of NO from pooled M. edulis pedal ganglia. 10, 20, and 30ul aliquots equivalent to 1, 2, and 3 mg equivalents of lipid extracted white willow bark engendered release of NO into the tissue bath at a peak concentrations of 4,10, and12 nM, respectively. N=3, mean$\pm$ SD.

Conclusions:

We have presently demonstrated selective evoked release of NO from pooled *Mytilus edulis* pedal ganglia by aliquots of a lipid extract of white willow bark but not by equivalent aliquots of two traditional water extracts of white willow bark. Based on accumulated prior art, and strongly supported by our current data sets the non-aqueous extraction procedure operationally eliminates water soluble salicin/salicylate-related chemical compounds from the assay system and provides compelling supporting evidence for the existence of a novel class of non-salicin/salicylate anti-inflammatory compounds in willow bark. These

findings are novel and unpredictable from prior art that also indicates an antagonist relationship between NSAID action and inducible NOS activation and NO production linked to inflammatory mediators such as prostanoid compounds.

Prior Art:

a. Healing Herbs page 371.

b. PDR for Herbal Medicines page 1112.